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January 31, 2014

Dr. Gupta

I am writing to express my concern about the 1 PPM water safety level for 4-Methylcyclohexane Methanol ("MCHM") established by the CDC. In my opinion, the CDC erred in using an antiquated and scientifically unacceptable calculation (Appendix 1) to extrapolate of data from animal studies to man. The animal dose cannot not be extrapolated to a human equivalent dose (HED) by a simple conversion based on body weight. Rather, the human equivalent dose should be derived from the body surface area (BSA) relationships between an animal species and humans (Appendix 2). BSA calculations are commonly used by pharmaceutical companies and the FDA to convert animal data to human doses used in phase I and II clinical trials.

The correct calculation is shown in Appendix 2. Using the BSA calculation, the human equivalent dose is 24 ppm. When the CDC uncertainty factors are applied, the safe dose is .024 ppm or 24 PPB in a 20 kg child. This concentration is much lower than the 1 PPM established by the CDC.

Since appropriate dose translation is the critical issue in the current spill, please have these calculations validated by the CDC and other toxicologists.

Thank you for your consideration in the matter.

Sincerely,

Dennis K. Flaherty, PhD.
Associate Professor
University of Charleston
School of Pharmacy

From the CDC website

Appendix 1

Few studies on this specialized chemical exist and most have been conducted on animals. Scientists used the limited information available about this chemical to calculate how much MCHM a person could ingest without resulting in adverse health effects. These calculations use uncertainty factors to take into account the differences between animals and people and to consider possible effects on special populations. An additional factor was applied to account for the limited availability of data. Based on the application of these uncertainty factors and the available research studies, scientists recommend a screening level of 1 part per million (1 ppm), or lower, of MCHM in drinking water.

CDC used the following calculation to establish a short-term screening level of 1 part per million (ppm) for the MCHM spill in the Elk River:

$$DW\ Advisory \leq \frac{NOEL \times BW}{UF \times Intake}$$

Where:

- DW Advisory = Drinking Water Advisory
- NOEL = No Observed Effect Level in the experimental species (100 mg/kg/day)
- BW = Body weight of a child (10 kg)
- UF = Uncertainty factors that address differences between animals and humans (10X), address differences accounting for sensitive humans (10x), and account for weaknesses in the toxicological database (10X).
- Intake = The estimated intake from drinking water of a 10 kg child (1 liter/day).

NOEL (mg/kg/d)	BW (kg)	UF (unitless)	Intake (L/day)	DW Advisory (mg/L or ppm)
100	10	1000	1	1

What studies were used in calculating the 1ppm recommendation?

We evaluated several studies from the manufacturer of MCHM to develop the recommended level of 1 ppm. These included the Pure MCHM 28-day oral study and the Crude MCHM LD-50 oral study.

We then extrapolated downwards to come up with the recommendation for a level that we believe would not be associated with any adverse health effects. This methodology is widely accepted and commonly used in environmental public health and risk assessment.

Pure MCHM 28-day Daily Oral Study Details - Rats received 0, 25, 100, and 400 mg/kg/day, 5 days a week, for 4 weeks. In this study, the administration of 400 mg/kg/day for 4 weeks was associated with erythropoietic, kidney, and liver effects, including increased liver weight, inflammation, and kidney tubular degeneration. The study determined that the No Observed Effect Level was 100 mg/kg/day.

Crude MCHM Acute Single Dose Oral Study Details - Male and female rats were dosed with 500, 1000, and 2000 mg/kg, followed by a 14-day observation period. The acute LD50 was calculated as 933 mg/kg for males and 707 mg/kg for females

Dose translation from animal to human studies revisited

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ABSTRACT As new drugs are developed, it is essential to appropriately translate the drug dosage from one animal species to another. A misunderstanding appears to exist regarding the appropriate method for allometric dose translations, especially when starting new animal or clinical studies. The need for education regarding appropriate translation is evident from the media response regarding some recent studies where authors have shown that resveratrol, a compound found in grapes and red wine, improves the health and life span of mice. Immediately after the online publication of these papers, the scientific community and popular press voiced concerns regarding the relevance of the dose of resveratrol used by the authors. The animal dose should not be extrapolated to a human equivalent dose (HED) by a simple conversion based on body weight, as was reported. For the more appropriate conversion of drug doses from animal studies to human studies, we suggest using the body surface area (BSA) normalization method. BSA correlates well across several mammalian species with several parameters of biology, including oxygen utilization, caloric expenditure, basal metabolism, blood volume, circulating plasma proteins, and renal function. We advocate the use of BSA as a factor when converting a dose for translation from animals to humans, especially for phase I and phase II clinical trials.—Reagan-Shaw, S., Nihal, M., Ahmad, N. Dose translation from animal to human studies revisited. *FASEB J.* 22, 659–661 (2007)

Key Words: drug dose conversion • body surface area

IN THE DEVELOPMENT OF NEW DRUGS to manage diseases, the scientific community relies heavily on animal studies that provide a framework for human clinical trials. Often, a drug that works well in animals is ostensibly not effective in humans. Several explanations exist for the lack of effectiveness.

One often-ignored explanation for drug ineffectiveness is the inappropriate translation of a drug dose from one animal species to another. The scientific as well as nonscientific communities seem to misunderstand the need for an appropriate method of allometric dose translation, especially when starting new animal or clinical studies. The calculations for determining starting dose in humans as extrapolated from animals

should use the more appropriate normalization of body surface area (BSA). This method was first introduced into medical oncology in order to derive a safe starting dose for phase I studies of anticancer drugs from preclinical animal toxicology data. Unfortunately, for a translational study, many convert the safe starting dose based on body weight alone, which can result in inappropriate comparisons between studies.

Two excellent examples of dissemination of misinformation are based on recent studies by Lagouge *et al.* (1) and Baur *et al.* (2), who suggest that the antioxidant resveratrol found in red wine can improve energy balance and protect against the diseases of aging. These studies gained popularity in the news media and subsequently were highlighted and critiqued by scientists around the world. Many media sources stressed that the doses used in mice could be interpreted to mean several hundred or even thousands of liters of wine per day in human equivalent doses (HEDs) (3–5). This serious misinterpretation resulted in skepticism of the scientific research. Unfortunately, the invalid calculations used to provide this interpretation demonstrate the ignorance of the scientific community and general public regarding appropriate methods of dose translation between species.

In this article, we provide pertinent information regarding appropriate methods for the translation of drug doses from animal studies to human studies for use in interpreting research results.

CORRECT DOSE CALCULATION: AN EXAMPLE

As described above, confusion and concerns emanated from a recent study by Baur *et al.* (2), where a dose of 22.4 mg/kg (body weight) of resveratrol was used in a mouse study on aging and obesity-related disorders. The media reported that a 60 kg human would have to consume 1344 mg of resveratrol per day in order to receive a like benefit, a serious misinterpretation of the research. Using an average of 2 mg resveratrol per bottle of wine (6), this calculation implies that a person

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would have to drink 672 bottles of red wine to approximate the resveratrol equivalent.

However, the Food and Drug Administration (7) has suggested that the extrapolation of animal dose to human dose is correctly performed only through normalization to BSA, which often is represented in mg/m^2 . The human dose equivalent can be more appropriately calculated by using the formula shown in Fig. 1. To convert the dose used in a mouse to a dose based on surface area for humans, multiply 22.4 mg/kg (Baur's mouse dose) by the K_m factor (3) for a mouse and then divide by the K_m factor (37) for a human (Table 1). This calculation results in a human equivalent dose for resveratrol of 1.82 mg/kg , which equates to a 109 mg dose of resveratrol for a 60 kg person. While not reasonably achievable through consumption of wine, this concentration may be provided through a daily oral supplement. We would like to emphasize that an appropriately calculated dose based on research in mice is achievable in humans. However, while supplements at this dose (109 mg) and higher are readily available in pill or capsule form for general public consumption, we do not advocate their usage.

THE USE OF BSA FOR DOSE TRANSLATION

Research has used BSA for conversion of drug doses between species for many years. The origin for understanding the relationship between the BSA of different species began in 1883 when observations that oxygen utilization and caloric expenditure were similar for various mammalian species and differently sized members of the same species when computed on the basis of body surface (8). These observations were then confirmed and applied to humans, which gave rise to expressing human basal metabolism in terms of BSA rather than body weight (9). Correlations between blood volume, circulating plasma proteins, and renal function with BSA in several species also have been illustrated (10). Thus, BSA correlates well with parameters of mammalian biology, which makes BSA normalization logical for allometric scaling of drug doses between species, given that the activity of most drugs corresponds to the relationship between the drug and some physiological process or function. Further, work by Freireich *et al.* (11) and Schein *et al.* (12) showed that for antineoplastic drugs, lethal doses to 10% (LD_{10}) of rodents and maximum tolerated doses (MTD) in nonrodents correlated with the human MTD when the doses were normalized to the same adminis-

Formula for Dose Translation Based on BSA	
HED (mg/kg) = Animal dose (mg/kg) multiplied by	$\frac{\text{Animal } K_m}{\text{Human } K_m}$

Figure 1. Formula for dose translation based on BSA.

TABLE 1. Conversion of animal doses to HED based on BSA

Species	Weight (kg)	BSA (m^2)	K_m factor
Human			
Adult	60	1.6	37
Child	20	0.8	25
Baboon	12	0.6	20
Dog	10	0.5	20
Monkey	3	0.24	12
Rabbit	1.8	0.15	12
Guinea pig	0.4	0.05	8
Rat	0.15	0.025	6
Hamster	0.08	0.02	5
Mouse	0.02	0.007	3

Values based on data from FDA Draft Guidelines (7). To convert dose in mg/kg to dose in mg/m^2 , multiply by K_m value.

tration schedule and expressed in terms of BSA in mg/m^2 . The authors of these studies pointed out that the evaluation of animal toxicity screening systems can be used as a tool to enable safe introduction of new drugs into humans, although the authors did not attempt to relate therapeutic doses in various species (11, 12).

When testing new drugs, the most appropriate species for assessing human risk is determined and then followed by toxicology studies. The K_m factor, body weight (kg) divided by BSA (m^2), is used to convert the mg/kg dose used in a study to an mg/m^2 dose. The K_m values based on average BSA calculations for human, baboon, dog, monkey, rabbit, guinea pig, rat, hamster, and mouse are shown in Table 1. For the purpose of initial clinical trials in healthy adult volunteers, the HED is calculated (Fig. 1) using BSA normalization of the animal dose where no observed adverse effects were observed (7). In phase I studies, data derived from animal models where the drug doses are tested until the LD_{10} is reached are used to derive the safe starting dose for human studies. The first human dose employed is the allometric conversion, based on BSA, of 1/10 of the LD_{10} for the relevant animal species (7). BSA normalization of doses must be used to determine safe starting doses of new drugs because initial studies conducted in humans, by definition, lack formal allometric comparison of the pharmacokinetics of absorption, distribution, and elimination parameters (13).

EXPANDED USE OF BSA IN CLINICAL MEDICINE

Some drugs are administered to patients based on estimations for desired plasma concentrations using available pharmacokinetics and pharmacodynamics data. Studies have suggested that the role of BSA could be expanded for drug dose calculation in an attempt to more accurately administer cytotoxic drugs to children. The major problem with using BSA as a factor for dose individualization is that BSA can only be estimated with a formula generally incorporating measures of body

weight and height. The customary approach for calculation of BSA uses the Du Bois height-weight formula: BSA (m^2) equals body weight (kg)^{0.425} multiplied by height (cm)^{0.725} multiplied by 0.007184, for which the constants were derived from only 9 patients (14;15). Subsequently, this formula has been challenged and re-evaluated in similar forms with updated constants. Alternative body-size measurements have been proposed, including lean body mass, ideal body weight, adjusted ideal body weight, and body mass index. However, scientific evidence does not favor one alternative formula over another (16–18). While the reliability of the Du Bois formula has been contested, the resultant approximation should be accepted not as a method of precise measurement but as a means of achieving more correct comparisons among species.

The question then becomes, what is the appropriate method for conducting human studies? Based on the allometric conversion of drug doses from animals that have undergone toxicology testing, the current practice in phase I trials involves calculating starting drug doses on the basis of the BSA of individual patients. The unfortunate side effect of this strategy is that unpredictable variations in effect are observed because BSA dosing does not take into account the complex process of drug elimination (19). Thus, overdosing can occur and is easily recognized, but underdosing can be just as frequent and leads to a reduced therapeutic result (19). Many researchers advocate abandoning this approach in favor of the administration of fixed drug doses that are calculated on the basis of an average 1.86 m^2 BSA, as calculated by one study (20). Dose refinement then would reflect the desired therapeutic outcome for individual patients with the added benefit of reducing errors in calculations and possibly reducing costs as well.

CONCLUSION

Unfortunately, the debate surrounding the use of BSA to adjust an individual patient's drug dose clouds the use of BSA for allometric conversion of doses and creates confusion in the scientific community as well as in the media. When animal studies such as those involving resveratrol are completed and media reports distort the dose translation between the study mice and the HED, misinformation regarding the effectiveness of resveratrol against a disease or condition hampers the significance of preclinical data. Understanding the more appropriate method based on BSA conversion for dose translation across species is an important issue for both the scientific community as well as the general public. Currently, BSA-based dose calculation is the most appropriate method and is far superior to the simple conversion based on body weight. However, a concerted effort toward designing more appropriate conversions that eliminate the problems associated with the BSA method is needed in order to improve therapeutic outcomes in trials. FJ

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